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$NiSO_4{\cdot}6H_2O$ as a new, efficient, and reusable catalyst for the α-aminophosphonates synthesis under mild and eco-friendly conditions

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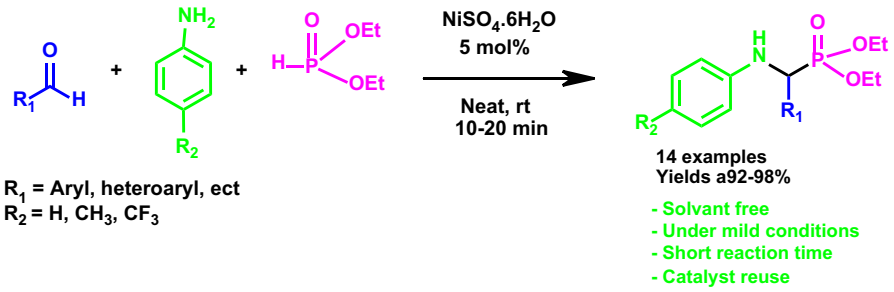
Abstract Nickel (II) sulfate hexahydrate is used for the first time as an efficient catalyst for the one-pot synthesis of α-aminophosphonates by three-component condensation reaction of aromatic aldehyde, primary amine, and diethylphosphite under mild and eco-friendly conditions. $NiSO_4{\cdot}6H_2O$ was used with a catalytic amount of 5 mol% at room temperature, without solvent in the reaction. A series of the desired α-aminophosphonates are obtained after a simple work-up procedure, with excellent yields (up to 92 %) within a short reaction time of 10–20 min in all cases. This heterogeneous catalyst was reused several times with the same activity. The present approach offers the advantages of a clean reaction, simple methodology, easy purification, and economic availability of the catalyst.

Graphical Abstract



Keywords Nickel (II) sulfate hexahydrate · α-Aminophosphonates · Solvent-free · Catalyst reuse · Green protocol

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Introduction

The α-aminophosphonate derivatives are well known as potential bioactive molecules for their multifarious therapeutic activities [1, 6, 17, 23, 24, 30]. They are used fruitfully in various domains, in agrochemistry as plant growth regulators, herbicides, insecticides, and fungicides [25, 26]. They are also known for their physical properties and are used as retardants for fire materials [2]. During the past few years, various methods have been developed for the synthesis of α-aminophosphonate. One of the main efficient known target reactions for developing new α-aminophosphonate derivatives is the Kabachnik–Fields reaction [11, 15]. The key step of this approach is the addition of the pentavalent phosphorus nucleophile to imine formed in situ between aldehyde and primary amine.

Similar methods are described [38] using variety of catalysts, Lewis acids, and others such as; TiO_2 [13], $SnCl_4$ [21], $ZnCl_2$ [39], $Sn(OTf)_2$ [12], $Cu(OTf)_2{\cdot}7H_2O$ [14], $BiNO_3{\cdot}5H_2O$ [8], BF_3–SiO_2 [28], $ZrOCl_2{\cdot}8H_2O$ or $ZrO(ClO_4)_2{\cdot}6H_2O$ [7], $Cp_2Zr(OSO_2C_4F_9)_2{\cdot}2H_2O$ [22], $Cd(ClO_4)_2{\cdot}H_2O$ [10], $CoCl_2{\cdot}6H_2O$ [18], Sulfamic-acid [27], TsCl [16], Fe/SWCNTs [31], $FeCl_3$ [29], etc. In spite of their advantages, these methods show some flaws. Among their disadvantages, we quote the low afforded yield, tedious work-up procedures, the long reaction time [22], large amount of catalyst [18], heating or addition of some bases as activator factor [31], and an excessive use of organic solvents presenting a serious danger to the environment [29].

The international tendency imposes the improvement of green and sustainable chemical processes, without generating waste. Therefore, researchers have elaborated new methods obeying environmental concerns which favor the development of new eco-friendly synthesis processes. These new paths must be designed to reduce the steps, using catalysis and avoid organic solvents, thereby contributing to the implementation of some greener criteria [3–5, 33–35].

In this paper, we propose a new soft and clean protocol for the synthesis of a set of α-aminophosphonate derivatives through multi-component condensation reaction in one pot, of an aldehyde, amine, and diethylphosphite, in the presence of a catalytic amount of $NiSO_4{\cdot}6H_2O$, under solvent-free conditions and without any activation (heating or base). The $NiSO_4{\cdot}6H_2O$ catalyst presents several advantages, no toxic, commercially available, cheap, easily removed, and recovered after achievement of the reaction, for an eventual recycling.

Experimental

General

All starting materials and reagents used in this study were obtained commercially from Aldrich and Acros and were used without purification. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica-gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent

and $KMnO_4$ solution as developing agents. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker spectrometers (300 MHz for ^1H, 75 MHz for ^{13}C). Chemical shifts were reported downfield from $CDCl_3$ ($\delta = 7.26$ ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent of $CDCl_3$ ($\delta = 77$ ppm) used as internal reference. Coupling constants (J) are given in Hertz. The following abbreviations classify the multiplicity: s = singulet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. Melting points were measured using Büchi Melting Point Model B-545.

General procedure for the synthesis of α-aminophosphonates (3a–3m)

In a round-bottomed flask, a mixture of aldehyde (1 mmol), aniline (1 mmol), and diethylphosphite (1.2 mmol), and a catalytic amount of $NiSO_4{\cdot}6H_20$ (5 mol%) were added. The mixture was stirred at room temperature for an appropriate time. The evolution of the reaction was monitored by TLC. After achieving the reaction, dichloromethane (2 × 10 ml) was added and the catalyst was filtered; water (10 ml) was then added. The organic layers were combined and dried over anhydrous sodium sulfate and removed under reduced pressure. The residue obtained was crystallized in hexane/ether to give desired pure crystals. All mentioned yields are those obtained after crystallization.

Spectral data of all the synthesized α-aminophosphonates (3a–3m)

Diethyl (phenyl)(phenylamino)methylphosphonate (**3a**) White crystalline solid. **Mp** 88 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\boldsymbol{\delta} = 1.13$ (*t*, 3H, $J = 7$ Hz, –OCH_2–$\mathbf{CH_3}$), 1.30 (*t*, 3H, $J = 7.1$ Hz, –OCH_2–$\mathbf{CH_3}$), 3.59–3.75 (1H, m, –$\mathbf{OCH_2}$ Me), 3.87–4.01 (1H, m, –$\mathbf{OCH_2}$–Me), 4.03–4.21 (2H, m, $\mathbf{OCH_2}$–Me), 4.74–4.82 (d, 1H, $J_{HP} = 24.3$ Hz, C**H**P), 6.61 (dd, 2H, $J = 8.6, 0.9$ Hz, $\mathbf{H_{Ar}}$), 6.71 (dd, 1H, $J = 10.5, 4.1$ Hz, $\mathbf{H_{Ar}}$), 7.12 (dd, 2H, $J = 8.5, 7.4$ Hz, $\mathbf{H_{Ar}}$), 7.22–7.43 (m, 3H, $\mathbf{H_{Ar}}$), 7.49 (d, 2H, $J = 7.2$, Hz, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\boldsymbol{\delta} = 146.28$) d, $J = 14.7$ Hz (136.00, 129.16, 128.59,127.83, 118.37, 113.83, 63.29 (d, $J_{CP} = 4.0$ Hz), 57.16, 55.16, 31.09, 16.61 (d, $J^3_{CP} = 18.3$), 16.53 (d, $J^3_{CP} = 5.8$ - Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\boldsymbol{\delta} = 23.24$ ppm.

Diethyl (4–nitrophenyl)(phenylamino) methylphosphonate (**3b**) Yellow crystalline solid. **Mp** 89.2 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\boldsymbol{\delta} = 1.13$ (t, 3H, $J = 7.1$ Hz, –OCH_2–$\mathbf{CH_3}$), 1.29 (t, 3H, $J = 7.1$ Hz, –OCH_2–$\mathbf{CH_3}$), 3.77–3.88 (m, 1H, –$\mathbf{OCH_2}$–CH_3), 3.90–4.05 (m, 1H, –$\mathbf{OCH_2}$–CH_3), 4.10–4.15 (m, 2H, $\mathbf{OCH_2}$–CH_3), 4.73–4.85 (d, 1H, $J_{HP} = 24.2$ Hz, CHP), 6.59–6.71 (m, 3H, $\mathbf{H_{Ar}}$), 6.73–6.85 (t, 2H, $J = 15.5$ Hz, $\mathbf{H_{Ar}}$), 7.12–7.19 (m, 2H, $\mathbf{H_{Ar}}$), 7.50–7.61 (d, 2H, $J_{HP} = 7.2$ - Hz, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\boldsymbol{\delta} = 146.28$ (d, $J = 14.7$ Hz(,136.09, 129.38, 128.82, 128.79, 128.12, 128.09, 118.60, 114.06, 63.56 (d, $J = 4.0$ Hz), 55.50, 56.99, 31.15 16.67 (d, $J^3_{HP} = 18.3$ Hz), 16.61 (d, $J^3_{HP} = 5.8$ Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\boldsymbol{\delta} = 22.71$ ppm.

Diethyl (4–chlorophenyl)(phenylamino) methylphosphonate (**3c**) White crystalline solid. **Mp** 86.8 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.18$ (t, 3H, $J = 7.0$ Hz, –OCH_2–$C\mathbf{H_3}$), 1.30 (t, 3H, $J = 7.0$ Hz, –OCH_2–$C\mathbf{H_3}$), 3.75–3.80 (m, 1H, –$OC\mathbf{H_2}$–Me), 3.92–4.06 (m, 1H, –$OC\mathbf{H_2}$–Me), 4.05–4.21 (m, 2H, $OC\mathbf{H_2}$–Me), 4.75 (d, 1H, $J_{HP} = 24.5$ Hz, C**H**P), 6.58 (dd, 2H, $J = 8.6, 0.9$ Hz, $\mathbf{H_{Ar}}$), 6.73(t, 1H, $J = 7.4$ Hz, $\mathbf{H_{Ar}}$), 7.13(dd, $J = 8.5, 7.4$ Hz, 2H, $\mathbf{H_{Ar}}$), 7.21–7.38 (m, 2H, $\mathbf{H_{Ar}}$), 7.44 (dd, $J = 8.6, 2.3$ Hz, 2H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 146.01$ (d, $J = 14.6$ Hz), 134.60, 133.70, 129.26 128.19, 128.89, 128.86, 118.66, 113.83, 63.38 (d, $J^2 = 6.8$ Hz), 56.60, 54.61, 30.94, 16.36 (d, $J^3 = 13.7$ Hz), 16.36 (d, $J^3 = 5.7$ Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 23.24$ ppm.

Diethyl(4-methoxyphenyl)(phenylamino) methylphosphonate (**3d**) White crystalline solid. **Mp** 103 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.14$ (t, 3H, $J = 7.0$ Hz, –OCH_2–$C\mathbf{H_3}$), 1.28 (t, 3H, $J = 7.0$ Hz, –OCH_2–$C\mathbf{H_3}$), 3.65–3.74 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 3.77 (s, 3H, –$OC\mathbf{H_3}$), 3.91 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.15 (m, 2H, $OC\mathbf{H_2}$–CH_3), 4.72 (d, $J = 24.4$ Hz, 1H, C**H**P), 6.58 (d, 2H, $J =$ Hz, $\mathbf{H_{Ar}}$), 6.66 (t, $J = 16.0$ Hz, 1H, $\mathbf{H_{Ar}}$), 6.85 (d, $J =$ Hz, 2H, $\mathbf{H_{Ar}}$), 7.07–7.13 (m, 2H, $\mathbf{H_{Ar}}$), 7.36–7.30 (m, 2H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 159.40$, 143.54 (d, $J = 15.4$ Hz), 129.24, 129.08, 129.01, 127.77, 127.73, 118.43, 114.16, 114.13, 63.39 (dd, $J^2 = 6.9, 3.9$ Hz), 56.45, 55.33, 54.43, 16.60 (d, $J^3 = 14.9$ Hz), 16.52 (d, $J^3 = 5.9$ Hz).**^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 23.47$ ppm.

Diethyl (4-biphenyl)(phenylamino) methylphosphonate (**3e**) White crystalline solid. **Mp** 158 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.18$ (t, 3H, $J = 7.1$ Hz, –OCH_2–Me), 1.33 (t, 3H, $J = 7.1$ Hz, –OCH_2–Me), 3.79 (m, 1H, –$OC\mathbf{H_2}$–Me), 3.90–4.08 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.06–4.26 (m, 2H, $OC\mathbf{H_2}$–CH_3), 4.68–4.97 (m, 2H, C**H** and N**H**), 6.66 (d, 2H, $J = 7.7$ Hz, $\mathbf{H_{Ar}}$), 6.74 (t, 1H, $J = 7.3$ Hz, $\mathbf{H_{Ar}}$), 7.16 (dd, $J = 8.3, 7.5$ Hz, 2H, $\mathbf{H_{Ar}}$), 7.21–7.51 (m, 3H, $\mathbf{H_{Ar}}$), 7.49–7.67 (m, 6H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 146.31$ (d, $J = 14.6$ Hz), 140.85, 140.80, 140.67, 135.04, 135.00, 129.32, 128.87, 127.83, 127.42, 127.39, 127.12, 118.57, 113.98, 63.35 (d, $J_{CP} = 6.9$ Hz), 56.82, 54.82, 16.37 (d, $J^3 = 16.9$ Hz), 16.37 (d, $J^3 = 5.8$ Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 23.12$ ppm.

Diethyl (phenyl)(p-tolylamino) methylphosphonate (**3f**) White crystalline solid. **Mp** 99 °C (*litt*. 101–102). **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.11$ (t, 3H, $J = 7.1$ Hz, –OCH_2–$C\mathbf{H_3}$), 1.28 (t, 3H, $J = 7.0$ Hz, –OCH_2–$C\mathbf{H_3}$), 2.18 (s, 3H, $C\mathbf{H_3}$–Ph), 3.64–3.72 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 3.90–3.98 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.08–4.15 (m, 2H, $OC\mathbf{H_2}$–CH_3), 4.70 (d, $J = 24.4$ Hz, 2H, C**H**P and N**H**), 6.50 (d, 2H, $J = 8.5$ Hz, $\mathbf{H_{Ar}}$), 6.90 (d, $J = 16.0$ Hz, 2H, $\mathbf{H_{Ar}}$), 7.23–7.35 (m, 3H, $\mathbf{H_{Ar}}$), 7.44–7.48 (m, 2H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 143.74$ (d, $J = 15.4$ Hz), 138.71, 138.68, 129.35, 128.27, 128.24, 127.56, 127.49, 127.30, 113.66, 63.01 (dd, $J^2 = 6.9, 2.9$ Hz), 57.01, 55.01, 20.06, 16.18 (d, $J^3 = 14.0$ Hz), 16.10 (d, $J^3 = 5.8$ Hz).**^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 23.36$ ppm.

Diethyl (4-nitrophenyl)(p-tolylamino) methylphosphonate (**3g**) Yellow crystallin. **Mp** 158 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): δ = 1.19 (t, 3H, *J = 7.0* Hz, –OCH_2–$C\mathbf{H_3}$), 1.30 (t, 3H, *J = 7.0* Hz, –OCH_2–$C\mathbf{H_3}$), 2.18 (s, 3H, $C\mathbf{H_3}$–Ph), 3.87–3.92 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.00–4.10 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.11–4.17 (m, 2H, –$OC\mathbf{H_2}$–CH_3), 4.72 (dd, *J = 10.5, 7.1* Hz, 1H, C**H**), 4.85 (dd, *J = 24.7, 7.0* Hz, 1H, N**H**), 6.47(d, *J* = 8.5 Hz, 2H, $\mathbf{H_{Ar}}$), 6.91 (d, 2H, *J* = 8.2 Hz, $\mathbf{H_{Ar}}$), 7.67 (dd, *J* = 8.8, 2.3 Hz, 2H, $\mathbf{H_{Ar}}$), 8.18 (dd, *J* = 8.8, 0.6 Hz, 2H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): δ = 147.69, 144.73 (d, *J* = 3.2 Hz), 143.33 (d, *J* = 14.6 Hz), 129.96, 128.79, 128.73, 128.54, 128.84, 126.84, 114.03, 63.58 (dd, J^2 = 23.8, 6.9 Hz), 55.41, 20.47, 16.59 (d, J^3 = 12.6, 5.8 Hz), 16.52 (d, J^3 = 5.8 Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): δ = 21.47 ppm.

Diethyl(4-chlorophenyl)(p-tolylamino) methylphosphonate (**3h**) White crystalline solid. **Mp** 119.5 °C **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): δ = 1.18 (t, 3H, *J = 7.1* Hz, –OCH_2–$C\mathbf{H_3}$), 1.31 (t, 3H, *J = 7.1* Hz, –OCH_2–$C\mathbf{H_3}$), 2.21 (s, 3H, $C\mathbf{H_3}$–Ph), 3.79–3.85 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 3.97–4.05 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.10–4.17 (m, 2H, $OC\mathbf{H_2}$–CH_3), 4.64–4.78 (m, 2H, C**H** +N**H**), 6.48 (d, 2H, *J = 8.5* Hz, $\mathbf{H_{Ar}}$), 6.93 (d, 2H, *J = 8.2* Hz, $\mathbf{H_{Ar}}$), 7.26 (m, 2H, $\mathbf{H_{Ar}}$), 7.43 (dd, *J = 12.0, 4.0* Hz, 2H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): δ = 143.85 (d, *J = 15.0* Hz), 134.84, 133.80, 133.76, 133.71, 129.83, 129.28, 128.21, 127.89, 127.86, 128.03, 114.06, 63.59 (dd, J^2 = *12.1, 7.0* Hz), 56.89, 54.89, 20.47, 16.59 (d, J^3 = *13.7* Hz), 16.52 (d, J^3 = *5.8* Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): δ = 22.69 ppm.

Diethyl(4-methoxyphenyl)(p-tolylamino) methylphosphonate (**3i**) White crystalline solid. **Mp** 99 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): δ = 1.14 (t, 3H, *J = 7.1* Hz, –OCH_2–$C\mathbf{H_3}$), 1.28 (t, 3H, *J = 7.1* Hz, –OCH_2–$C\mathbf{H_3}$), 2.18 (s, 3H, $C\mathbf{H_3}$–Ph), 3.66–3.74 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 3.77 (s, 3H, –$OC\mathbf{H_3}$), 3.91–3.96 (m,1H, –$OC\mathbf{H_2}$–CH_3), 3.99–4.15 (m, 2H, $OC\mathbf{H_2}$–CH_3), 4.70 (d, *J = 24.5* Hz, 2H, C**H**P + N**H**), 6.49 (d, 2H, *J = 8.4* Hz, $\mathbf{H_{Ar}}$), 6.92 (dd, *J = 16.0, 8.5* Hz, 4H, $\mathbf{H_{Ar}}$), 7.26–7.39 (m, 2H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): δ = 159.20, 144.20 (d, *J = 15.4* Hz), 129.76, 129.08, 129.01, 127.92, 127.88, 127.68, 114.12, 63.38 (dd, J^2 = *6.9, 2.9* Hz), 56.74, 55.34, 54.72, 20.49, 16.63 (d, J^3 = *14.0* Hz), 16.55 (d, J^3 = *5.8* Hz).**^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): δ = 23.59 ppm.

Diethyl (4-biphenyl)(p-tolylamino) methylphosphonate (**3j**) White crystalline solid. **Mp** 140 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): δ = 1.17 (t, 3H, *J = 7.1* Hz, –OCH_2–$C\mathbf{H_3}$), 1.32 (t, 3H, *J = 7.1* Hz, –OCH_2–$C\mathbf{H_3}$), 2.21 (s, 3H, $C\mathbf{H_3}$–Ph), 3.77–3.83 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 3.97–4.05 (m, 1H, –$OC\mathbf{H_2}$–CH_3), 4.12–4.20 (m, 2H, –$OC\mathbf{H_2}$–CH_3), 4.82 (d, 1H, *J = 24.5* Hz, C**H**P), 6.56 (d, 2H, *J = 8.3* Hz, $\mathbf{H_{Ar}}$), 6.94 (d, 2H, *J = 8.3* Hz, $\mathbf{H_{Ar}}$), 7.26–7.38 (m, 1H, $\mathbf{H_{Ar}}$), 7.42–7.47 (m, 2H, $\mathbf{H_{Ar}}$), 7.54–7.60 (m, 6H, $\mathbf{H_{Ar}}$). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): δ = 144.15 (d, *J = 15.1* Hz), 140.72 (d, *J = 4.3* Hz), 135.16, 135.13, 129.82, 128.87, 128.37, 128.30, 127.81, 127.44, 127.41, 127.38, 127.12, 110.10, 63.44 (t, J^2 = *6.9* Hz), 57.16, 55.17, 20.50, 16.62 (d, J^3 = *17.0* Hz), 16.55 (d, J^3 = *5.8* Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): δ = 23.24 ppm.

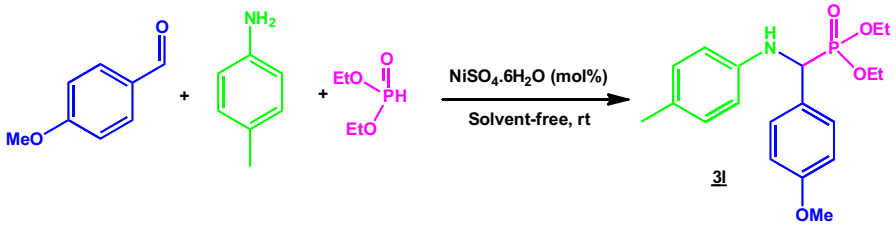
Diethyl(phenyl)(4-trifluoromethyl)phenylamino) methylphosphonate (**3k**) White crystalline solid. **Mp** 140 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.12$ (t, 3H, $J = 7.0$ Hz, –OCH_2–C**H_3**), 1.31 (t, 3H, $J = 7.1$ Hz, –OCH_2–C**H_3**), 3.61–3.70 (m, 1H, –O**CH_2**–CH_3), 3.90–4.08 (dp, $J = 10.1, 7.1$ Hz, 1H, –O**CH_2**–CH_3), 4.10–4.20 (m, 2H, O**CH_2**–CH_3), 4.79 (dd, 1H, $J = 24.2$, 7.5 Hz, Ph–C**H**), 5.16–5.31 (m, 1H, N**H**), 6.62 (d, 2H, $J = 8.5$ Hz, **H_{Ar}**), 7.26–7.40 (m, 5H, **H_{Ar}**), 7.49 (dd, $J = 7.7, 2.1$ Hz, 2H, **H_{Ar}**). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 148.90$ (d, $J = 14.4$ Hz), 135.13 (d, $J = 3.0$ Hz), 128.91, 128.87, 128.38, 128.34, 127.90, 127.83, 126.68, 126.63, 113.16, 63.75 (dd, $J^2 = 22.9, 7.0$ Hz), 56.77, 54.77, 16.59 (d, $J^3 = 19.0$ Hz), 16.51 (d, $J^3 = 5.8$ Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 22.54$ ppm.

Diethyl(4-methoxyphenyl)(4-trifluoromethylphenylamino) methylphosphonate (**3l**) White crystalline solid. **Mp** 111 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.15$ (t, 3H, $J = 7.0$ Hz, –OCH_2–C**H_3**), 1.31 (t, 3H, $J = 7.1$ Hz, –OCH_2–C**H_3**), 3.63–3.72 (ddd, $J = 10.1, 8.3, 7.1$ Hz, 1H, –O**CH_2**–CH_3), 3.80 (s, 3H, –O**CH_3**), 3.95 (dt, $J = 10.1, 7.1$ Hz, 1H, –O**CH_2**–CH_3), 4.13 (m, 2H, –O**CH_2**–CH_3), 4.73 (dd, 1H, $J = 23.8, 7.6$ Hz, C**H**P), 5.15 (dd, $J = 9.7, 7.8$ Hz, 1H, –N**H**), 6.63 (d, 2H, $J = 8.5$ Hz, **H_{Ar}**), 6.90 (d, 2H, $J = 8.5$ Hz, **H_{Ar}**), 7.26–7.40 (m, 4H, **H_{Ar}**). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 159.60$, 148.16 (d, $J = 14.3$ Hz), 128.97, 126.96, 126.67, 114.35 (d, $J = 2.3$ Hz), 113.19, 63.70 (dd, $J^2 = 24.1, 7.0$ Hz), 56.10, 55.38, 54.08, 16.61 (d, $J^3 = 13.9$ Hz), 16.54 (d, $J^3 = 5.8$ Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 22.77$ ppm.

Diethyl(4-chlorophenyl)(4-trifluoromethylphenylamino) methylphosphonate (**3m**) White crystalline solid. **Mp** 129 °C. **^{1}HNMR** (**300** MHz, **$CDCl_3$**, **25** °C): $\delta = 1.18$ (t, 3H, $J = 6.9$ Hz, –OCH_2–C**H_3**), 1.32 (t, 3H, $J = 7.1$ Hz, –OCH_2–C**H_3**), 3.72–3.81 (m, 1H, –O**CH_2**–CH_3), 3.96–4.01 (m, 1H, –O**CH_2**–CH_3), 4.04–4.18 (m, 2H, –O**CH_2**–CH_3), 4.70 (dd, 1H, $J = 24.4, 7.3$ Hz, C**H**P), 5.16 (dd, 1H, $J = 10.2, 7.5$ Hz, –N**H**), 6.60 (d, 2H, $J = 8.6$ Hz, **H_{Ar}**), 77.28–7.43 (m, 6H, **H_{Ar}**). **^{13}CNMR**: (**75** MHz, **$CDCl_3$**, **25** °C): $\delta = 148.61$ (d, $J = 14.2$ Hz), 134.24 (d, $J = 3.9$ Hz), 134.19, 133.96, 133.92, 129.19, 129.12, 126.76, 126.71, 113.19, 63.71 (dd, $J^2 = 11.2, 7.0$ Hz), 56.27, 54.27, 16.60 (d, $J^3 = 13.9$ Hz), 16.53 (d, $J^3 = 5.7$ Hz). **^{31}P NMR**: (**121** MHz, **$CDCl_3$**, **25** °C): $\delta = 21.87$ ppm.

Results and discussion

The aim of this study is to develop an efficient and eco-friendly protocol to access α-aminophosphonate compounds with a green chemistry approach. Firstly, we have explored the reactivity and the activation threshold of $NiSO_4 \cdot 6H_2O$ as heterogeneous catalyst for the three-component condensation. For this study, we chose these three components, *p*-methoxy-benzaldehyde, *p*-toluidine, and diethyl phosphite (Scheme 1). It is the ideal combination for our study, the *methoxy*-group on *para*-position of the aromatic ring of the aldehyde reduces the electrophilicity, and methyl



Scheme 1 General reaction

Table 1 Effect of catalytic amount of $NiSO_4{\cdot}6H_2O$ on the synthesis of **3i**

Entry[a]	$NiSO_4{\cdot}6H_2O$ (mol%)	Time (min)	Yield (%)[b]
1	Without	120	NR
2	20	60	97
3	15	60	96
4	10	60	93
5	**5**	**10**	**98**
6	2	120	Traces

The bold values indicate the best results

[a] Reaction conditions: *p*-methoxylbenzaldehyde (1 mmol), *p*-toluidine (1 mmol), diethylphosphite (1.2 mmol), $NiSO_4{\cdot}6H_2O$ (mol%), at room temperature and solvent-free conditions

[b] Isolated yield after crystallization with ether/hexane

group on *para*-position of the aromatic ring of the toluidine reduces the nucleophilicity.

We have used a mixture of 1 equivalent of aldehyde, 1 equivalent of aniline and 1.2 equivalent of diethylphosphite and different catalytic rates of $NiSO_4{\cdot}6H_2O$ from 20 to 2 mol%, in a solvent-free condition at room temperature. The reactions were monitored by TLC analysis. The reaction mixtures were quenched, by simple extraction and the desired pure products have been recovered by simple crystallization in ether/hexane. The obtained results are summarized in Table 1.

The α-aminophosphonate **3i** is obtained in high yields (93 % ≤ yield ≤ 98 %) (Table 1, entries **2**–**5**) using a catalytic amount from 20 to 5 mol% of $NiSO_4{\cdot}6H_2O$. The results described in Table 1 show a significant effect of the amount of the catalyst. It is found that the decrease of the catalytic amount of $NiSO_4{\cdot}6H_2O$ leads to a considerably increased reaction rate, from 1 h with 20 mol% to 10 min using just 5 mol% of this catalyst (Table 1, entries **2**–**5**). For quantities of catalysts between 10 and 20 mol%, the reaction time is 60 min and the yields range from 93 % ≤ yield ≤ 97 % (Table 1, entries **2**–**4**). Furthermore, without a catalyst, no product formation (Table 1, entry **1**) and with 2 mol% the traces of **1** are detected (Table 1, entry **6**). These results affirm not only the utility of this catalyst to achieve the three-component condensation but also its efficiency with an optimal catalytic amount of 5 mol%.

The activity of the recycled catalyst was also examined under the optimized conditions (Scheme 1). After the completion of reaction, $NiSO_4{\cdot}6H_2O$ was removed

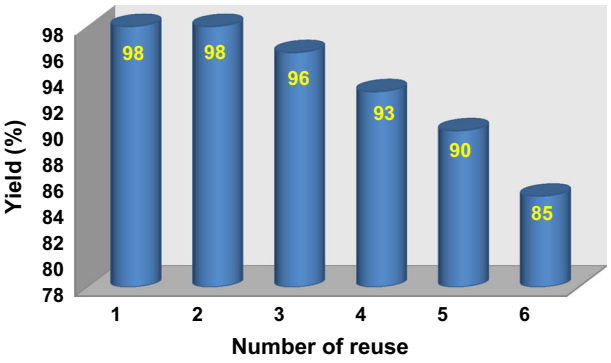
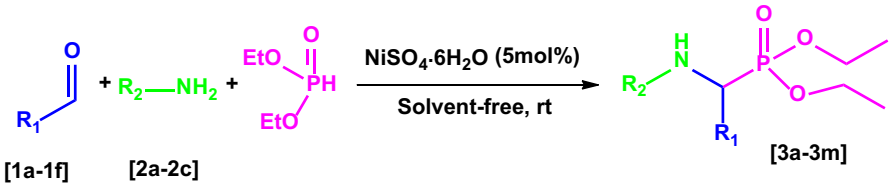


Fig. 1 Reusing of the $NiSO_4{\cdot}6H_2O$ catalyst



Scheme 2 Application of the reaction with new catalyst $NiSO_4{\cdot}6H_2O$

by filtration, washed with methanol, and directly reused in another reaction. The recovered catalyst was reused for six consecutive cycles without any significant loss in catalytic activity, proving its efficiency. Until the fifth reuse, the α-aminophosphonate **3l** is obtained with excellent yield between 90 % < yield < 98 %. However, from the sixth recycling, a loss of the catalytic performance of $NiSO_4{\cdot}6H_2O$ is recorded, the recovered yield decreases to 85 % (Fig. 1).

To validate this new catalyst ($NiSO_4{\cdot}6H_2O$) and extend its use and its catalytic reactivity, the reaction conditions are applied on a series of variously substituted aldehydes coupled with diverse aromatic amines in the presence of diethylphosphite and 5 mol% of $NiSO_4{\cdot}6H_2O$ at room temperature without a solvent (Scheme 2).

The α-aminophosphonates [**3a–3m**] are obtained after a simple work-up procedure (extraction-crystallization) with excellent yields (up to 92 %) within 10–20 min. The results are presented in Table 2. The structures of all products are determined by ^{1}H ^{13}C and ^{31}P NMR analysis.

The results in Table 2 show various aldehydes and amines as reactants were screened with 5 mol% of $NiSO_4{\cdot}6H_2O$ in Kabachnik–Fields reaction, and good-to-excellent yields (>92 %) were obtained in very short time ($t < 20$ min). The reaction between aniline and aromatic aldehydes substituted by electron-withdrawing groups provides excellent yields in 20 min, due to mesomeric and inductive effects in the presence of diethylphosphate (Table 2, entries **1–5**). When aniline is substituted with electron donating, the catalysis with $NiSO_4{\cdot}6H_2O$ (5 mol%) leads to α-aminophosphonate compounds with excellent yields an even faster time of 10 min (Table 2, entries **6–10**). The use of 4-trifluoroaniline is carried out with a

Table 2 Scope of the $NiSO_4 \cdot 6H_2O$ catalyst in the synthesis of a series of α-aminophosphonates

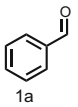
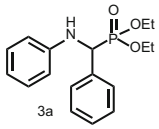
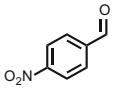
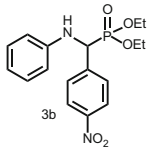
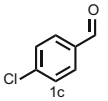
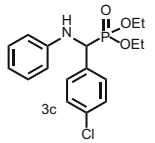
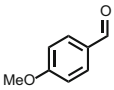
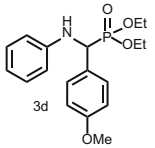
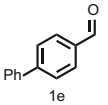
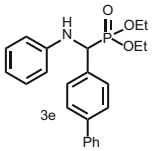
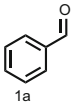
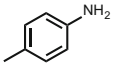
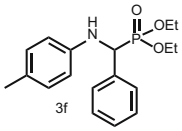
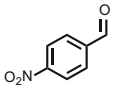
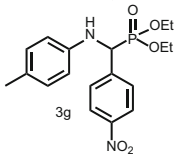
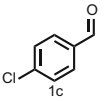
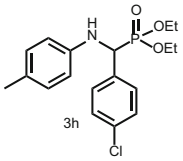
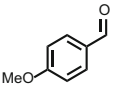
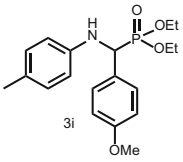
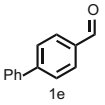
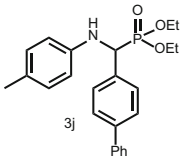
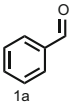
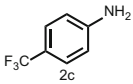
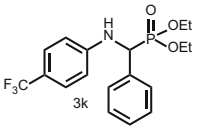
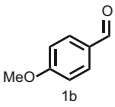
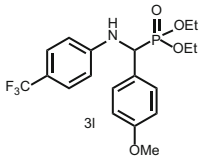
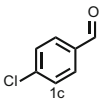
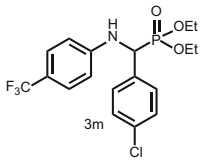
Entry [a]	Aldehyde	Amine	Product	Time (min)	Yield (%)[b]
1	 1a	 2a	 3a	20	96
2	 1b	2a	 3b	20	92
3	 1c	2a	 3c	20	94
4	 1d	2a	 3d	20	96
5	 1e	2a	 3e	20	97
6	 1a	 2b	 3f	10	97
7	 1b	2b	 3g	10	95
8	 1c	2b	 3h	10	96
9	 1d	2b	 3i	10	98

Table 2 continued

Entry [a]	Aldehyde	Amine	Product	Time (min)	Yield (%)[b]
10	 1e	2b	 3j	10	98
11	 1a	 2c	 3k	15	96
12	 1b	2c	 3l	20	96
13	 1c	2c	 3m	20	94
14	 1f	2a	--	120	--

[a] All reactions were carried out with 1 mmol of aldehyde, 1 mmol of amine, 1.2 mmol of diethylphosphite and 5 mol% of $NiSO_4{\cdot}H_2O$

[b] Isolated yield after crystallization with ether/hexane

high yield in spite of the property of the electron-withdrawing group (*–CF3*); this group could have reduced the nucleophilicity of the amine, nevertheless the α-amino phosphonates are obtained in 15–20 min with a yield >94 %, due, definitely, to the efficiency of the catalyst $NiSO_4{\cdot}6H_2O$ (Table 2, entries **11**–**13**).

In the presence of $NiSO_4{\cdot}6H_2O$ as a catalyst, the α-aminophosphonates are readily obtained, without substantial involvement of the electronic effects of various substituents of amine in the condensation reaction. We observe a slight acceleration of the reaction when using anilines substituted by an electron-donating group on the *–para* potion of the aromatic ring with a reaction time of 10 min, compared with the electron-withdrawing groups with a reaction time of 20 min. Albeit, with the 3-furyl-benzaldehyde, the corresponding α-aminophosphonate is not formed after

Table 3 Comparison of $NiSO_4{\cdot}6H_2O$ with various catalysts

Entry	Catalyst (mol%)	T (°C)	Time	Yield (%)	References
1	**$NiSO_4{\cdot}6H_2O$ (5)**[a]	**rt**	**20 min**	**98**[b]	
2	TiO_2(20)	50	4 h	98	[13]
3	$Cp_2Zr(OSO_2C_4F_9)_2{\cdot}2H_2O$(5)	rt	2.5 h	90	[22]
4	Sulfamic-acid (20)	rt	2 h	87	[27]
5	$Cu(OTf)_2$ (5)/Ligand	rt	6 h	90	[36]
6	BF_3SiO_2 (5)/[bmim][HCl]	rt	5 min	97	[28]
7	Fe/SWCNTs (5)	50	60 min	95	[31]
8	Acid 1-hexanesulphonic (10)/ultrasonication	rt	12 min	94	[20]

[a] Reaction conditions: 4-methoxylbenzaldehyde (1mmom), aniline (1 mmol), diethylphosphite (1.2 mmol), $NiSO_4{\cdot}6H_2O$ (5 mol%), ambient temperature, 20 min

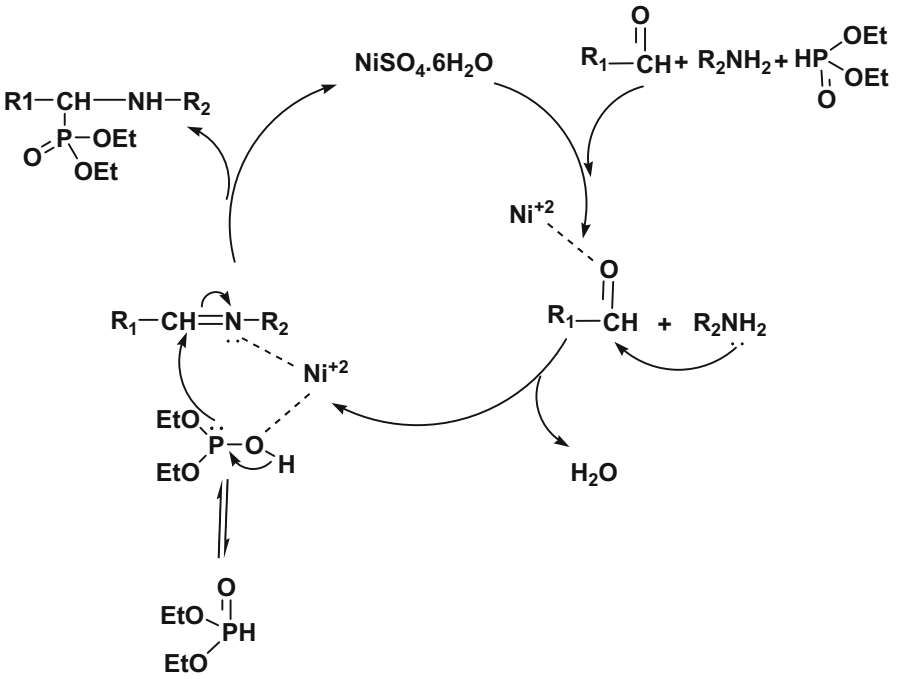
[b] Isolated yield after crystallization with ether/hexane

120 min of stirring. This fact is probably due to the electronic effects related to the presence of oxygen in this position (Table 2, entry **14**).

As a supplementary, and in order to delineate the efficiency of use of the $NiSO_4{\cdot}6H_2O$ as novel robust catalyst, we have compared it to other described protocols selected from the literature using diverse catalysts to elaborate the Kabachnik–Fields reaction for the synthesis of α-aminophosphonates. Our comparison is based on the following parameters: temperature, duration, and yield. The results are reported in Table 3.

The results of the literature described in Table 3 show that with 20 mol% TiO_2, the reaction is carried out at 50 °C with a 98 % yield in 4 h (Table 3, entry **2**). The sulfamic-acid catalyst (20 mol%) led to α-aminophosphonate compounds with 87 % yield after 2 h of stirring at room temperature (Table 3, entry **4**). Using 5 mol% $Cu(OTf)_2$ combined to *bis*-fluoro-oxazolines, as ligand, gives the α-amino phosphonates with 90 % yield at room temperature in 6 h (Table 3, entry **5**). In the presence of 5 mol% of BF_3SiO_2, the reaction is completed in 5 min in ionic liquid [bmim] [HCl] (Table 3, entry **6**). The use of iron-doped single-walled carbon nanotubes (Fe/SWCNT) (5 mol%) for 60 min at 50 °C gives a 95 % yield (Table 3, entry **7**). The 1-hexanesulphonique acid and sodium salt (10 mol%) under ultrasound as source of activation leads to the desired product with a yield of 94 % in 12 min (Table 3, entry **8**). Recently, the complex $Cp_2Zr(OSO_2C_4F_9)_2{\cdot}2H_2O$ (5 mol%) was used as a catalyst for the same reaction at room temperature; the yield is 90 % in 2.5 h (Table 3, entry **3**). In Table 3, several catalysts were evaluated by for the synthesis of α-aminophosphonates via Kabachnik–Fields reaction. Comparing the reaction conditions with the $NiSO_4{\cdot}6H_2O$ catalyst, it is found that the reaction time is longer, the catalytic rate is higher, and more expensive. The reaction is carried out in the presence of solvents, heating, or the addition of some bases as activator factor. Moreover, the catalyst must be prepared in some instances.

The present methodology reveals many benefits of the use of $NiSO_4{\cdot}6H_2O$ (5 mol%) as a new robust heterogeneous catalyst for the synthesis to α-aminophosphonates by one-pot, three-component condensation. The reaction is carried in a maximum time of 20 min, with an excellent yield 98 %, without solvent and without heating activation or introducing additives (Table 3, entry **1**).



Scheme 3 The proposed mechanism of the one-pot reaction catalyzed by $NiSO_4{\cdot}6H_2O$

On the basis of the experimental results and the literature which describe plausible mechanisms for the formation of α-aminophosphonates [19, 32, 37], we propose one possibility in Scheme 3. So, in our case, the pathway most probable is via the imine formation, knowing that the aromatic amine reacts very quickly with the benzaldehyde and derivatives [9]. It is estimated that, in the first time, nickel coordinates the oxygen of the aldehyde and creates a good electrophilic site followed by a nucleophilic attack of primary amine to form in situ an imine and the elimination of the water formed. Then, the nickel coordinates again, with both nitrogen of the imine and the oxygen of diethylphosphite in parallel to accelerating the nucleophilic reaction of the phosphite on the imine to give the expected product.

Conclusion

We have described a new catalyst, the nickel (II) sulfate hexahydrate, to access the α-aminophosphonates by a one-pot, three-component condensation: aldehyde, amine, and diethyl phosphate, at room temperature, under solvent-free conditions.

This catalyst presents several advantages such as low catalytic amount of 5 mol%, short reaction times between 10 and 20 min, easy purification, and the desired products are recovered with excellent chemical yields. $NiSO_4{\cdot}6H_2O$ is a catalyst that is commercially available, cheap, stable, easily recovered, and it can be reused six times keeping the same catalytic efficiency. It is in favor of this new

catalyst, high level of activity at room temperature with low catalytic rate, without solvent or activation; it is also an inexpensive recyclable catalyst. The approach described is simple and environmentally friendly.

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